REMARKS

Examination of claims 21-24 and 26-51 is reported in the present Office action. Applicants have added new claim 52. Support for claim 52 is found at least at page 6, lines 20-21 of the specification. Claims 21-24 and 26-51 stand rejected under 35 U.S.C. § 102(e) and under 35 U.S.C. § 103(a). Each of these rejections and objections is addressed below.

Rejections under 35 U.S.C. § 102(e)

Claims 21-24 and 26-51 are rejected under 35 U.S.C. 102(e) as being anticipated by Goldstein et. al. (US Patent 5,899,937) (referred to hereafter as "Goldstein"). Applicants traverse the rejection. The Examiner states that Goldstein teaches a method of manufacturing a bioprosthetic heart valve that uses endothelial cells and further states that although Goldstein does not deem it necessary to use endothelial cells, this is not an inclusive bar against using endothelial cells in forming heart valves. See, Office Action at page 3-4.

Applicants submit that Goldstein does not anticipate the method of the instant invention. The instant invention teaches a method of manufacturing a bioprosthetic heart valve comprising seeding the matrix with *isolated* myofibroblasts and *isolated* endothelial cells. Seeding the matrix with *isolated* cells means that each cell type is separated into an isolated single-type population which is substantially free of other cell types or compositions with which it naturally occurs. The claim term "isolated" is unambiguously defined in the specification (page 2, lines 12-23, of the specification. Specifically for the endothelial cells, the culture medium is changed to remove fibroblasts and smooth muscle cells. When the seeding is done with a mixture of isolated myofibroblasts and isolated endothelial cells, each cell type is separated into an isolated single-type population before the cells are mixed (page 2, lines 20-23, of the specification).

Thus, the claims require a very specific and well-defined population of cells. In contrast, Goldstein describes dermal fibroblasts taken from upper thigh skin and cultured (col. 16, lines 1-11 of Goldstein). Such explants contain a mixture of a number of different cell types and no isolation of any particular cell type is described by this reference.

Moreover, claim 21 requires a completely different cell type than that described by Goldstein. The method of Goldstein provides a heart valve seeded with dermal fibroblasts (See *e.g.*, col. 1, lines 24-28; col. 1, line 61-col. 2, line 4; col. 2, lines 40-44; col. 6, lines 58-59; col. 14, lines 37-39 of Goldstein). Isolated myofibroblasts are not dermal fibroblasts. Myofibroblasts differ from dermal fibroblasts in a number of significant ways such as protein production and contractile function. These are differentiated cells, which are resistant to dedifferentiation during culture prior to and after implantation into a recipient individual (page 1, lines 26-27, of the specification). Although dermal fibroblasts may differentiate into myofibroblasts upon exposure to appropriate conditions, they are not encompassed by the claim term. As is clearly delineated in the specification, isolated myofibroblasts are obtained from sold heart leaflet tissue (page 2, lines 14-15, of the specification) or after differentiation of fibroblasts from other tissue sources (e.g., vascular, dermal) to a myofibroblast phenotype. The specification states "Fibroblasts from these sources acquire the myofibroblast phenotype with the use of dynamic tissue culture conditions and/or cell signaling factors " (page 9, lines 15-16, of the specification. The Goldstein process is completely different from the claimed methods in several ways, not the least of which is the phenotype/differentiation state of the cells used to seed the valve. Goldstein does not teach seeding with myofibroblasts, and further Goldstein does not teach seeding with *isolated* myofibroblasts and *isolated* endothelial cells which have been separated from other cell types or compositions from which the cells naturally occur.

Applicants submit that claims 21-24 and 26-51 are not anticipated by Goldstein and respectively request withdrawal of this rejection under § 102(e).

Rejection under 35 U.S.C. § 103(a)

Claims 21-24 and 26-51 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Goldstein in view of Bishopric et al. (US 5,855,620) (referred to hereinafter as "Bishopric") and Vacanti et al. (US 6,348,069) (referred to hereinafter after as "Vacanti"). Applicants traverse the rejection.

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces the claimed invention; (2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and (3) the prior art reveals that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness.

The Combination Does Not Produce the Claimed Invention

Goldstein teaches a method of manufacturing a bioprosthetic heart valve that uses isolated dermal fibroblasts [and isolated endothelial cells] for repopulation (See, col. 1, lines 24-28; col. 1, line 61-col. 2, line 4; col. 2, lines 40-44; col. 6, lines 58-59; col. 14, lines 37-39 of Goldstein).

Bishopric discloses a method of decellularization where the matrix can be readily colonized by both fibroblasts and endothelial cells as well as other types of cells such as dermal

fibroblasts, cardiac fibroblasts, myofibroblasts, smooth muscle cells, and autologous endothelial cells and fibroblasts derived from host tissues including fat and peripheral vein (See, col. 6, lines 5-7; col. 7, lines 59-63). Bishopric states that neonatal rat cardiac fibroblasts (NMC) were isolated (plated out to be 95% fibroblasts and 5% smooth muscle). This reference also fails to isolate and rigorously characterize each specific cell type used for seeding.

Vacanti discloses a method for making a cell-matrix construct for use as a heart valve comprising implanting into an animal a fibrous matrix formed of a synthetic biodegradable polymer having seeded a mixture of cells selected from endothelial cells, myofibroblasts, skeletal muscle cells, vascular smooth muscle cells, myocytes, fibromyoblasts, and ectodermal cells. Cells to be implanted are dissociated using standard techniques such as digestion with collagenase, trypsin or other protease solutions. Example 1 uses a mixed cell population including myofibroblasts and endothelial cells. In addition to containing myofibroblasts and endothelial cells, a "mixed cell population" harvested from sheep heart valves without any other manipulation contains other undefined cell types in undefined amounts. Thus, this reference also fails to describe or suggest a population of isolated myofibroblasts as required by the claims.

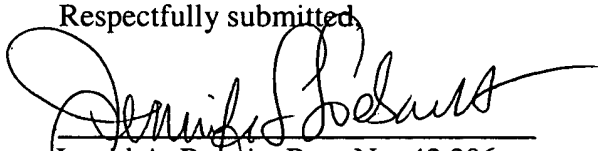
The combination of references falls short of suggesting all the requirements of the claimed invention and falls short of providing motivation to one of skill in the art to use the precisely defined cell populations in the method as claimed. Therefore, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants submit that the claims are now in condition of allowance and such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Enclosed is a petition of extension of time and a check in the amount of the required fee. The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 21486-027DIV).

Respectfully submitted,



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